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Evolution of paced QRS and QTc intervals in children with epicardial pacing leads

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Abstract: Aims : Permanent ventricular pacing in children is associated with ventricular dysfunction due to asynchronous activation. It is unclear whether paced QRS intervals increase disproportionately over time, which could potentially cause ventricular dysfunction. Methods : A total of 52 children, with bipolar steroid-eluting epicardial leads implanted at a median age of 5.6 years (0.0-17.4), was analyzed and followed up to 12.2 years (median 3.7). Patients were subdivided in two groups: right (RV, n = 21) and left (LV, n = 31) ventricular pacing. To correct for age, standard deviation scores (Z-scores) for paced QRS and QTc intervals were calculated from published standard-ECG norm-values. As a measure for individual paced QRS and QTc interval changes, a regression slope coefficient (inclinei) was calculated for each patient's course. Results : Mean Z-scores for paced QRS intervals at first and last follow-up were 4.7 ± 1.2 and 4.9 ± 0.9 for group RV, 4.4 ± 1.1 and 4.8 ± 1.1 for group LV. Inclinei of paced QRS (group RV: 0.038 [-0.27-0.12], group LV: 0.147 [-0.05-0.30]; $p = 0.07$) and QTc intervals (group RV: 0.026 [-0.08-0.06], group LV: 0.023 [-0.04-0.09]; $p = 0.63$) did not differ between both groups and indicated limited interval changes over time. Conclusion : Neither epicardial pacing of the right nor left ventricle caused disproportionate paced QRS or QTc interval increases over time. An age-related prolongation of the electrical activation unlikely causes ventricular dysfunction

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Abstract *Aims* Permanent ventricular pacing in children is associated with ventricular dysfunction due to asynchronous activation. It is unclear whether paced QRS intervals increase disproportionately over time, which could potentially cause ventricular dysfunction. *Methods* A total of 52 children, with bipolar steroid-eluting epicardial leads implanted at a median age of 5.6 years (0.0–17.4), was analyzed and followed up to 12.2 years (median 3.7). Patients were subdivided in two groups: right (RV, n=21) and left (LV, n=31) ventricular pacing. To correct for age, standard deviation scores (Z-scores) for paced QRS and QTc intervals were calculated from published standard-ECG norm-values. As a measure for individual paced QRS and QTc interval changes, a regression slope coefficient (incline_i) was calculated for each patient's course. *Results*

Mean Z-scores for paced QRS intervals at first and last follow-up were 4.7 ± 1.2 and 4.9 ± 0.9 for group RV, 4.4 ± 1.1 and 4.8 ± 1.1 for group LV. Incline_i of paced QRS (group RV: 0.038 [−0.27–0.12], group LV: 0.147 [−0.05–0.30]; $p=0.07$) and QTc intervals (group RV: 0.026 [−0.08–0.06], group LV: 0.023 [−0.04–0.09]; $p=0.63$) did not differ between both groups and indicated limited interval changes over time. *Conclusion* Neither epicardial pacing of the right nor left ventricle caused disproportionate paced QRS or QTc interval increases over time. An age-related prolongation of the electrical activation unlikely causes ventricular dysfunction.

Key words permanent pacing – epicardial lead – children – ECG – paced QRS interval – cardiac asynchrony

Introduction

Ventricular pacing in children is known to alter inter- and intraventricular conduction delay [1]. The paced ventricle is depolarized first, followed by a slow electrical activation through the myocardium of the unpaced ventricle. Therefore, the paced QRS complex resembles that of a right or left ventricular conduction delay, depending on the pacing site. On surface ECG, this produces a prolongation of the paced QRS, and

indirectly of the QTc interval. Thus, uncoordinated contraction of the ventricles results in asynchrony, decreased stroke volume, and adverse myocyte remodeling. Over time, this may contribute to structural and functional changes [2–5]. Theoretically, these structural changes, along with fibrosis surrounding the pacing lead, and a physiologic increase of the ventricular mass in a growing child, may result in further slowing of the electrical activation, and therefore increased intraventricular conduction delay.

There is no information whether permanent epicardial pacing in children results in a possible disproportionate increase of the paced QRS intervals on surface electrocardiogram (ECG) over time. Therefore, we evaluated the evolution of paced QRS and QTc intervals in children with permanent epicardial ventricular pacing.

Patients and methods

■ Patient population

With hospital ethical committee approval and informed consent, we retrospectively reviewed charts and electronic pacemaker databases of children who received a permanent epicardial ventricular pacing system. Bipolar steroid-eluting epicardial leads (Medtronic CapSureEpi 10366 or 4968, Medtronic, Inc, Minneapolis, MN, USA) were implanted at the right ventricular apex or the left ventricular free wall. They were connected to various pulse generators. In case of a lead exchange, follow-up was completed at that point. From the date of exchange, the child was included as a new patient ($n=3$). Children with transvenous pacing systems, those with less than 90% ventricular pacing, as well as children with less than three ECGs during follow-up were excluded. Patients were subdivided into two groups: those with right (*group RV*) and those with left ventricular epicardial pacing leads (*group LV*).

■ Paced QRS and QTc interval

ECG documentation directly after implantation and at various follow up times consisted of hard copies. Surface 12-channel ECGs were recorded with a Mac®5000 System (GE Medical Systems, Milwaukee, WI, USA) either in our institution or at outpatient visits by the referring cardiologist. Measurements of paced QRS and QTc intervals automatically were performed by computed electrocardiographic system analysis of intervals, as well as manually measured from lead V5 by one author (M.T.). In case of inconsistent results, intervals were double-checked (U.B.). The paced QRS interval was defined as the length of time from the beginning of the pacing spike to the end of the QRS complex. No pronounced latency from the pacemaker stimulus to the onset of the earliest paced QRS complex was seen (<40 ms). No drugs known to prolong QRS or QTc intervals were given to any patient included into the study.

The standardized deviation-score (Z-score) for paced QRS and QTc intervals were calculated from

published standard-ECG values of healthy children [6] to correct for age. For calculation of the age corrected paced QRS the following formula was used:

$$\frac{\text{paced QRS}_{\text{measured}} - \text{norm mean QRS}_{\text{ad}}}{\text{norm standard deviation of QRS}_{\text{ad}}}$$

where QRS_{ad} is the age-dependent QRS in healthy children.

For each patient's measurement (paced QRS or QTc-interval), the corresponding Z-score is therefore the difference of the measurement from the age-dependent norm mean, expressed in units of norm standard deviations.

■ Global left ventricular function

Echocardiographic data were assessed by experienced cardiologists and retrospectively derived from electronic patient charts. To determine global left ventricular function, the fractional shortening (parasternal long axis) and ejection fraction (apical 4-chamber view, Simpson equation) at first and last follow-up were noted.

■ Statistical analysis

Data are expressed as either median ([interquartile range], range) or mean (\pm standard deviation) depending on distribution pattern of the data evaluated by the Kolmogorov-Smirnov test. A p-value <0.05 was considered statistically significant.

To determine an individual persistent change of paced QRS and QTc intervals over time, slope coefficients from a regression over individual repeated measurements (incline_i) were calculated for each patient's course. Mann-Whitney U tests were used for analyzing differences in continuous variables between independent groups. For group differences in categorical variables, the chi-squared test was used. Using the Wilcoxon signed rank test, intra-individual changes in continuous variables between the two follow-up intervals were evaluated. To determine a possible influence of the age at implantation and total time of follow-up on the incline_i of paced QRS- and QTc-intervals a regression analysis was performed. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS for Windows, Version 14.0.1, Inc., Chicago, IL, USA).

Results

Demographic and surgical data, clinical characteristics

Demographic data, clinical characteristics, pacemaker data and underlying cardiac anatomy of group RV ($n=21$) and group LV ($n=31$) are given in Tables 1 and 2. All children with a congenital heart defect underwent prior cardiac surgery. In a

total of 47 children (90.4%) ventricular pacing was seen in 100% of the time. Even though there was a difference between median ages at lead implantation for right or left ventricular pacing, it was not statistically significant ($p=0.095$). No significant difference between group RV and group LV was seen in the distribution of children with a structural normal heart or congenital heart disease ($p=0.85$) and the underlying indication for permanent pacing ($p=0.89$).

Table 1 Demographic data, clinical characteristics, and pacemaker data at implant

	All Patients($n=52$)	Group RV ($n=21$)	Group LV ($n=31$)
Gender (male/female), $n=$	27/25	8/13	18/13
At lead implantation ^a			
Age (y)	5.6 (0.0–17.4)	3.3 (0.0–16.4)	7.0 (0.0–17.4)
Weight (kg)	18 (1.0–61.6)	15.5 (2.8–61.6)	20.0 (1.0–61.0)
Total time of follow up (y) ^a	3.7 (0.7–12.2)	4.0 (0.9–12.2)	3.2 (0.7–11.1)
Epicardial leads, $n=(\%)$			
Medtronic 10366	18 (35)	10 (48)	8 (26)
Medtronic 4968	34 (65)	11 (52)	23 (74)
Ventricular pacing mode, $n=(\%)$			
Unipolar pacing mode	40 (77)	18 (86)	22 (71)
Bipolar pacing mode	12 (23)	3 (14)	9 (29)
Pacing mode, $n=(\%)$			
VVI/VVIR	10 (19)	5 (24)	5 (16)
DDD	42 (81)	16 (76)	26 (84)
Indications, $n=(\%)$			
Congenital AVB	14 (27)	6 (29)	8 (26)
Post-operative AVB	25 (48)	10 (48)	15 (48)
Acquired AVB	5 (10)	3 (14)	3 (10)
SSS	1 (2)	–	1 (3)
Post-operative SSS	4 (8)	2 (10)	2 (7)
Sinus node dysfunction	2 (4)	–	2 (7)

^a Data are given as medians (range)

AVB atrioventricular block; SSS sick sinus syndrome

Table 2 Underlying cardiac anatomy and concomitant or previous surgery of the study cohort

		All Patients ($n=52$)	Group RV ($n=21$)	Group LV ($n=31$)
Cardiac anatomy, $n=$	Structurally normal heart	19	8	11
	Atrioventricular septal defect	6	2	4
	Ventricular septal defect (VSD)	7	3	4
	D-TGA with VSD	5	2	3
	L-TGA	2	1	1
	Tetralogy of Fallot	2	2	–
	Ebstein anomaly	1	1	–
	Complex single ventricle	10	2	8
Cardiac surgery, $n=$		33 (63%)	13 (62%)	20 (65%)
	Fontan operation	10	3	7

TGA Transposition of the great arteries

Table 3 Absolute values, Z-scores and regression slope coefficients (incline) for paced QRS and QTc intervals for group RV and group LV

Variable	Group RV (n=21)	Group LV (n=31)	p-value
Paced QRS (ms)			
First follow-up	148 (108–228)	150 (100–210)	0.84 ^c
Last follow-up	158 (138–212)	160 (120–224)	0.99 ^c
Paced QTc (ms)			
First follow-up	495 (424–535)	490 (421–588)	0.39 ^c
Last follow-up	488 (439–564)	489 (421–588)	0.63 ^c
Z-score for paced QRS ^a			
First follow-up	4.6 (2.5–7.9)	4.2 (1.7–6.9)	0.59 ^c
Last follow-up	4.7 (3.9–6.9)	4.5 (3.1–7.2)	0.63 ^c
Z-score for paced QTc ^a			
First follow-up	1.8 (1.0–2.0)	1.7 (1.0–3.0)	0.37 ^c
Last follow-up	1.7 (1.0–2.8)	1.7 (1.0–3.0)	0.55 ^c
Incline _i for paced QRS ^b	0.038 [–0.27–0.12]	0.147 [–0.05–0.30]	0.07 ^c
Incline _i for paced QTc ^b	0.026 [–0.08–0.06]	0.023 [–0.04–0.09]	0.63 ^c

Data are given as ^a medians (range) or ^b medians [interquartile range]; ^c not significant

■ Paced QRS and QTc intervals on surface ECG at various follow-up times

During follow up, ECGs of the children were available at median interval of 1.3 years (0.3–2.2). At first and last follow-up, absolute values as well as Z-scores for paced QRS and QTc intervals did not differ significantly for group RV and group LV. Furthermore, the incline_i of paced QRS and QTc intervals did not differ significantly between both groups (Table 3). Low values for the incline_i of paced QRS and QTc intervals indicated little individual interval changes during the whole observation period (Fig. 1).

Regression analysis revealed no significant impact of the child's age at epicardial lead implantation or of the total time of follow up on the incline_i of QRS intervals (lead implant: $R^2=0.004$, $p=0.65$; follow up: $R^2=0.014$, $p=0.41$) (Figs. 2 and 3). Furthermore, no significant impact on the incline_i of QTc intervals was observed (lead implant: $R^2=0.041$, $p=0.15$; follow-up: $R^2=0.004$, $p=0.21$). Additionally, differences in the incline_i of paced QRS and QTc intervals with regard to the underlying heart defect or indication for permanent pacing were analyzed. No significant difference was observed for the presence or absence of a congenital heart defect (QRS interval: $p=0.63$ and QTc interval: $p=0.49$), nor the underlying indication, especially congenital or post-operative atrio-ventricular block (QRS interval: $p=0.56$ and QTc interval: $p=0.85$).

Separate analysis between single or dual chamber pacing modes revealed no difference for absolute paced QRS values at first (143 ± 21 ms vs 156 ± 26 ms,

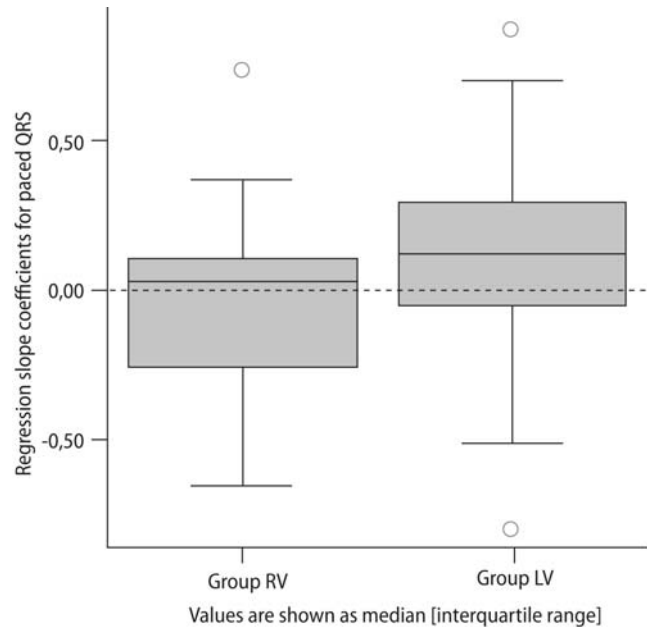


Fig. 1 Boxplot of individual regression slope coefficients (incline) of paced QRS intervals indicating little interval changes during follow-up. Incline_i of paced QRS for group RV were centered near 0 (median=0.038), but showed a tendency to be skewed towards negative values

$p=0.09$) or last follow-up (156 ± 21 ms vs 167 ± 24 ms, $p=0.18$). Likewise, no difference was seen for absolute paced QTc values at first (482 ± 39 ms vs 494 ± 32 ms, $p=0.39$) or last follow-up (485 ± 38 ms vs 497 ± 35 ms, $p=0.25$). Moreover, no difference was seen for the incline_i of paced QRS and QTc intervals between single or dual chamber pacing modes (QRS interval: $p=0.63$ and QTc interval: $p=0.39$).

■ Global left ventricular function

In 39 of the 52 children (75%), global left ventricular function was analyzed. Fractional shortening at a first and last follow-up did not differ for group RV ($37\pm 6\%$ vs $34\pm 6\%$; $p=0.14$) or group LV ($35\pm 6\%$ vs $37\pm 5\%$; $p=0.14$). Similarly, ejection fraction did not differ at a first and last follow-up for group RV ($58\pm 5\%$ vs $54\pm 7\%$; $p=0.15$) or group LV ($58\pm 6\%$ vs $58\pm 7\%$; $p=0.75$). In the remaining 13 children, global systemic ventricular function could not be assessed due to the underlying cardiac anatomy (complex single ventricle ($n=10$), L-transposition of the great arteries ($n=2$), D-transposition of the great arteries after Senning repair ($n=1$)). The echocardiographic aspect of the systemic ventricular function was judged as good by experienced cardiologists in all 13 children.

Fig. 2 Correlation between age at epicardial lead implantation and individual regression slope coefficients (incline) for paced QRS intervals did not show a significantly influence ($p=0.65$)

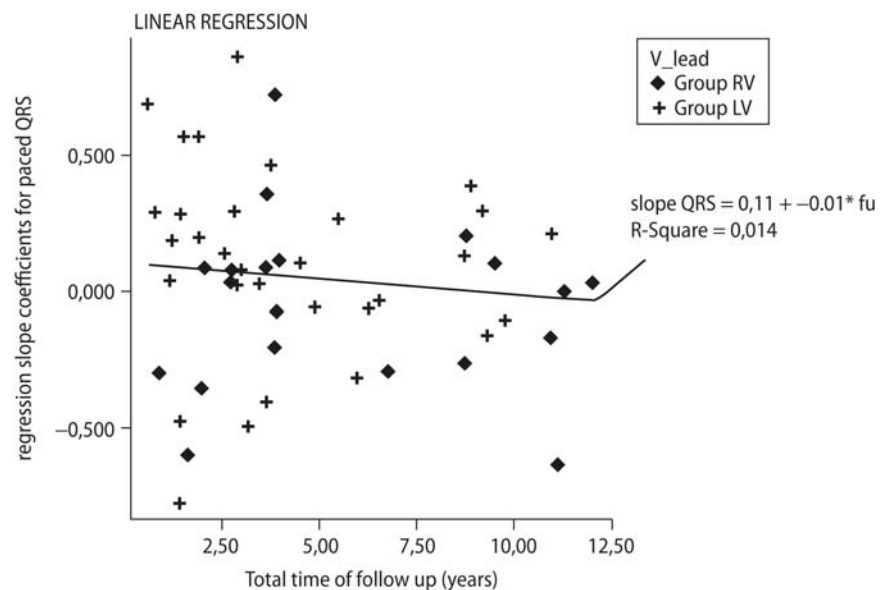
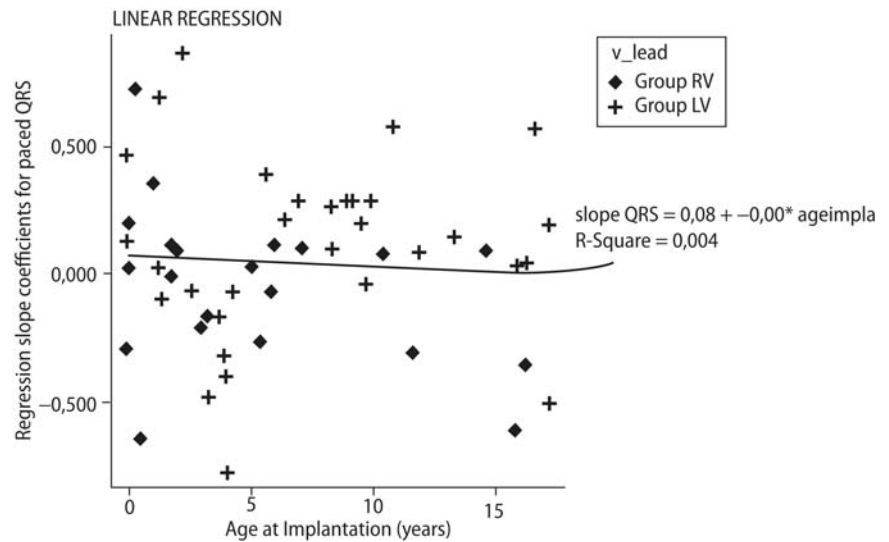


Fig. 3 Correlation between the total time of follow-up and individual regression slope coefficients (incline) for paced QRS intervals did not show a significantly influence ($p=0.41$)

Discussion

Permanent ventricular pacing provides increasing evidence of asynchronous ventricular electrical activation, leading to conduction delay and induction of ventricular dysfunction. The risk of heart failure due to impaired ventricular pump function increases over time [7, 8]. There is no information whether paced QRS intervals increase disproportionately in the growing heart of pediatric patients, which could be an additional cause for long-term cardiac morbidity.

The right ventricular apex used to be the gold standard for ventricular pacing. Recognition of an

abnormal electrical activation and the resulting impaired ventricular pump function has led to controversies about the optimal ventricular pacing site [9, 10]. Recent literature favors the left ventricle, as it seems to result in a more synchronous activation of the left ventricle and improved hemodynamics [11, 12]. Different abnormalities have been described to be associated with deterioration of the ventricular pump function. In children with chronic right ventricular apex pacing, histopathologic abnormalities by endomyocardial biopsy have been found that point to diminished function, as observed clinically [13]. Moreover, an asymmetric hypertrophy with increased wall thickness due to higher workload in the

late activated area of the left ventricle has been observed after chronic right ventricular pacing [14, 15].

However, there is little knowledge whether these abnormalities cause an increasing prolongation of the paced QRS interval on surface electrocardiogram. An animal model has examined the effect of workload on electrophysiology [16]. Conduction velocity was significantly reduced in the late-activated areas. As the mechanism of this change remained unclear, the authors suggested a theory of remodeled Purkinje fiber electrophysiology. Even though tissue fibrosis as a possible cause of reduced conduction velocity was not found, it is a main determinant. Changes in the amount and type of fibrous tissue in the interstitium can alter conduction velocity [17], and therefore lead to conduction delay. Marked tissue fibrosis has been observed in the use of transvenous electrodes [18, 19]. Since the introduction of steroid eluting leads, the inflammatory response at the electrode-tissue interface has been diminished. This has consistently led to low pacing thresholds in transvenous as well as epicardial leads [20–22]. The electrode-epimyocardial tissue reaction has hereby been limited, but not totally eliminated.

A relationship between conduction delay and impaired left ventricular function was demonstrated in clinical trials. In children with long-term pacing at the right ventricular apex, left ventricular short axis fractional area of change decreased by 0.2% for every 1-ms increase in QRS duration [7]. In adults, a progressive prolongation of the paced QRS intervals during follow-up has been shown to be a predictor for congestive heart failure [23], whereas corrected electrical asynchrony with narrowed QRS intervals by simultaneous right and left ventricular pacing improved cardiac output [24, 25].

As discussed above, all the processes and changes of the ventricles themselves, including asymmetrical hypertrophy, reduced conduction velocity, and tissue fibrosis can alter electrical activation, and as a consequence, lead to conduction delay. A further deterioration of these processes due to chronic ventricular pacing over time, and the physiologic increase of the ventricular mass in a growing child can be anticipated. Theoretically, this would result in an increasingly delayed electrical activation through the myocardium and therefore disproportional prolongation of the paced QRS intervals on surface ECG in children with permanent pacing.

In our study, we analyzed a total of 52 children with permanent epicardial ventricular pacing followed up to 12.2 years. We subdivided our population into two groups for further analysis: those with right and left ventricular epicardial pacing. The main finding was that there was no significant pro-

longation of age-correlated paced QRS or QTc intervals over time in children with permanent epicardial pacing, regardless of the pacing site. No significant impact of a congenital heart disease or the underlying indication for permanent pacing was detected. Remarkably, a slight even though not significant trend of regression slope coefficients for paced QRS skewed towards negative values in patients with right ventricular pacing was observed, and remains unclear.

Furthermore, no significant impact on global left ventricular function was observed between the first and last follow-up in children with two-chamber anatomy and either right or left ventricular epicardial pacing. However, regional ventricular dyssynchrony is rather obtained by tissue Doppler imaging or strain echocardiography [26–28]. Thus, potential right or left ventricular dyssynchrony might have evolved even though fractional shortening and ejection fraction of the left ventricle remained unchanged.

Considering all the arguments for a possible increase in intraventricular conduction delay over time, it seems comforting that permanent epicardial pacing in a growing child is associated with a rather homogenous age-dependent prolongation of paced QRS intervals. A disproportionate increase is an unlikely factor for the asynchronous electrical activation in permanent epicardial pacing. However, the pathophysiologic changes and regional ventricular dyssynchrony might not strongly correlate with a widening of QRS intervals on surface ECG [29].

■ Limitation of the study

A main limitation of this study is its retrospective design with regard to completeness and reproducibility of the collected variables. In order to avoid potential selection bias, every child with epicardial pacing leads implanted in our institution was included in the cohort of our study. Those children with less than three ECGs during follow-up due to missing documentation were excluded. The main variables paced QRS and QTc intervals were objective measurements performed by computed electrocardiographic system analysis of intervals, as well as manually measured by a single cardiologist from lead V5. This causes a low probability for misclassification, and allows for a precise statement.

A further limitation is the assessment of global left ventricular function by conventional measurements. An analysis with advanced techniques, such as tissue Doppler imaging or strain echocardiography, might have revealed regional ventricular dyssynchrony.

Conclusion

Permanent epicardial ventricular pacing results in a prolongation of the paced QRS intervals. However, it is associated with a homogenous age-dependent prolongation of paced QRS and QTc intervals up to a maximum observation period of 12.2 years. An age-related prolongation of the electrical activation un-

likely aggravates or causes ventricular dysfunction. However, regional ventricular dyssynchrony might not alter ECG measurements. Further prospective studies are required with documentation of the evolution of paced QRS and QTc intervals as well as simultaneous measurement of ventricular dyssynchrony by advanced technique echocardiography.

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